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The effects of proton exposure on neurochemistry and behavior

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Abstract

Future space missions will involve long-term travel beyond the magnetic field of the Earth, where astronauts will be exposed to radiation hazards such as those that arise from galactic cosmic rays. Galactic cosmic rays are composed of protons, α particles, and particles of high energy and charge (HZE particles). Research by our group has shown that exposure to HZE particles, primarily 600 MeV/n and 1 GeV/n ^{56}Fe, can produce significant alterations in brain neurochemistry and behavior. However, given that protons can make up a significant portion of the radiation spectrum, it is important to study their effects on neural functioning and on related performance. Therefore, these studies examined the effects of exposure to proton irradiation on neurochemical and behavioral endpoints, including dopaminergic functioning, amphetamine-induced conditioned taste aversion learning, and spatial learning and memory as measured by the Morris water maze. Male Sprague–Dawley rats received a dose of 0, 1.5, 3.0 or 4.0 Gy of 250 MeV protons at Loma Linda University and were tested in the different behavioral tests at various times following exposure. Results showed that there was no effect of proton irradiation at any dose on any of the endpoints measured. Therefore, there is a contrast between the insignificant effects of high dose proton exposure and the dramatic effectiveness of low dose (<0.1 Gy) exposures to ^{56}Fe particles on both neurochemical and behavioral endpoints.
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Keywords: Neurochemistry; Behavior; Proton exposure; Radiation; Spatial learning; Memory

1. Introduction

Future missions in space (such as a mission to Mars) may involve long-term travel beyond the magnetic field of the Earth, subjecting astronauts to radiation hazards posed by solar flares and galactic cosmic rays, consisting of protons, α particles, and particles of high energy and charge (HZE particles). Exposure of astronauts to these radiation sources may affect their ability to successfully complete mission requirements. It therefore becomes important to determine which particles have deleterious effects on brain neurochemistry and behavior, and the nature of these effects.

Research from our laboratories has shown that exposure of rats to HZE particles, primarily 600 MeV or 1 GeV ^{56}Fe, can produce profound deficits in behavior and neurochemistry, even at relatively low doses (0.1 Gy). These changes are similar to those seen in aged animals (Joseph et al., 1998, 2000). Exposing rats to HZE particles disrupts the functioning of the dopaminergic system and behaviors mediated by this system, such as motor performance (Joseph et al., 1992), spatial learning and memory (Shukitt-Hale et al., 2000, 2003), amphetamine-induced conditioned taste aversion learning (Rabin et al., 1998, 2000, 2002a), conditioned place preference (Rabin et al., 2001, 2003), and operant conditioning (fixed-ratio bar pressing) (Rabin et al., 2002b). These deficits have been shown as early as 12 h following 0.10–1.0 Gy radiation (e.g., motor performance) and as long as 180 days post-irradiation (e.g., oxotremorine-enhancement of K^+-evoked release of dopamine from striatal slices) (Joseph et al., 1992). Since these changes may be due to permanent alternations in the functioning of the dopaminergic neurons, many of these behaviors fail to show recovery of function following exposure. One study showed that exposure to 1 Gy of ^{56}Fe particles

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produced equivalent disruptions in the acquisition of an amphetamine-induced conditioned place preference, which is dependent upon the integrity of the dopaminergic system, when the rats were tested at 3, 7, or 16 weeks following irradiation (Rabin et al., 2003).

Since protons can make up a significant portion of the radiation spectrum, it became important to study the neurochemical and behavioral effects of exposure to high energy protons, to see if they were similar to those seen following exposure to HZE particles. Therefore, these studies examined the effects of exposure to proton irradiation on the following neurochemical and behavioral endpoints: dopaminergic functioning measured via oxotremorine-enhancement of K^+-evoked release of dopamine from striatal slices, amphetamine-induced conditioned taste aversion (CTA) learning, and spatial learning and memory as measured by the Morris water maze (MWM) in male Sprague–Dawley rats who had received a dose of 0, 1.5, 3.0 or 4.0 Gy of 250 MeV protons at Loma Linda University.

2. Methods

2.1. Animals

A total of 88 male Sprague–Dawley rats (Taconic Farms, Germantown, NY) weighing 250–275 g at the start of the experiment were used in this study (48 for the conditioned taste aversion learning and 40 for the Morris water maze/neurochemical assessments). The animals were 2 months of age when exposed to radiation using the accelerator at Loma Linda University in Riverside, CA. The rats were exposed to 0, 1.5, 3.0, or 4.0 Gy whole-body irradiation (22 rats in each group) with proton particles (250 MeV) at a dose rate of approximately 1 Gy/min. The rats were irradiated one at a time in well-ventilated plastic holders that minimized movement. The rats were positioned in the line of the beam so that their heads were located in the center of the beam. Dosimetry was provided by the staff of the accelerator facility.

2.2. Procedures

2.2.1. Amphetamine-induced conditioned taste aversion learning

Forty-eight rats ($N = 12$ each at 0, 1.5, 3.0, or 4.0 Gy proton dose) were tested 3 days following radiation exposure in the CTA test. A CTA is produced when a novel tasting conditioned stimulus is paired with an unconditioned stimulus. Rats were first adapted to a 23.5-h water deprivation schedule on which they received water for 30 min/day for 5–7 days. On the conditioning day (Day 6), the water bottle was replaced by a calibrated drinking tube containing a 10% sucrose solution and intake during the 30-min drinking period was measured. Immediately following the drinking period, the rats were administered the unconditioned stimulus, an injection of amphetamine (3 mg/kg, ip). Twenty-four hours later, the rats were again presented with the calibrated drinking tubes containing 10% sucrose for 30 min and their intake recorded. A CTA is shown as a reduction in test day sucrose intake compared to conditioning day intake. Previously, we have shown that exposing rats to 1 Gy of ^{56}Fe particles blocks the acquisition of amphetamine-induced CTA (i.e., greater sucrose intake than non-irradiated rats) 3 days following irradiation (Rabin et al., 1998).

2.2.2. Morris water maze

Forty rats ($N = 10$ each at 0, 1.5, 3.0, or 4.0 Gy proton dose) were shipped to the USDA, Human Nutrition Research Center on Aging at Tufts University (HNRCA) in Boston, MA, 4 days following radiation, where they were allowed to acclimate for 6 weeks before testing in the MWM and neurochemical assessments of dopaminergic functioning. At the HNRCA, the rats were individually housed in hanging wire mesh cages with ad libitum access to food and water in a colony maintained at constant temperature (21 °C+/−1°), on a 12-h light/dark cycle.

The MWM is a learning paradigm that requires the rat to use spatial learning to find a hidden platform (10 cm in diameter) submerged 2 cm below the surface of the water in a circular black fiberglass pool (134 cm in diameter × 50 cm in height), filled to a depth of 30 cm with water maintained at 23 °C, and to remember its location from the previous trial. The maze is placed in a room with the lights dimmed, with extramaze cues on the walls. Accurate navigation is rewarded with escape from the water onto the platform, which the rat uses distal cues to effectively locate.

Morris water maze testing was performed daily for 4 consecutive days, 6 trials/day. At the beginning of each trial, the rat was gently immersed in the water at one of three randomized start locations (located 90° apart on the perimeter of the pool). Each rat was allowed 60 s to escape onto the platform; if the rat failed to escape within this time, it was guided to the platform. Once the rat reached the platform, it remained there for 10 s. At the end of each trial, the rat was towel-dried, returned to its home cage for approximately 15–20 min (during which the remaining rats were tested) before being returned to the maze for its next trial. On days 1–3, the platform was placed in the northwest quadrant (quadrant 4). Trial 6 on days 2 and 3 was a probe trial where the platform was removed from the pool and the rat swam in the maze for 60 s to measure search strategies and spatial bias. On day 4, a reversal test was performed wherein the platform position was changed to the southeast quadrant (quadrant 2), diagonally opposite to

the training quadrant, in order to assess the ability of the rats to relearn a new platform location; the sixth trial was a probe trial.

Performance on each trial was videotaped and analyzed with image tracking software (HVS Image, Hampton, England). This software provided dependent measures such as latency (s), distance swam (cm), and speed (cm/s) to find the hidden platform, as well as information on the probe trials, such as time spent in the area where the platform had been previously located. For a more detailed description of the maze and the paradigm used, see Shukitt-Hale et al. (2000). We have previously shown that rats irradiated with 1.5 Gy of ^{56}Fe radiation have impairments in spatial learning and memory behavior when tested one month following exposure, manifested as increased latencies to find the hidden platform, particularly on the fourth day when the platform is moved to the opposite quadrant from the one where the platform was originally placed at the beginning of the test (Shukitt-Hale et al., 2000).

2.2.3. Dopamine release

Dopaminergic functioning was measured in 24 of the above rats four weeks after they were tested in the Morris water maze ($N = 6$ each at 0, 1.5, 3.0, or 4.0 Gy proton dose) via oxotremorine-enhancement of K^+-evoked release of dopamine (K^+-ERDA) from striatal slices as previously described (Joseph et al., 1992). Briefly, cross cut striatal slices (300 μm) from each rat were prepared using a McIlwain tissue chopper. The slices were placed in small glass vials containing modified Krebs-Ringer basal release medium (BRM) that had been bubbled for 30 min with 95% O_2/5% CO_2 and which contained (in mM) $NaHCO_3$ 21, glucose 3.4, NaH_2PO_4 1.3, EGTA 1, $MgCl_2$ 0.93, NaCl 127 and KCl 2.5 (low KCl) (pH 7.4). They were then placed in the perfusion chambers where they were maintained at 37 °C and perfused with the BRM for 30 min. Following this equilibration period, the medium was then switched to one containing (in mM) KCl 30, $CaCl_2 \cdot 2H_2O$ 1.26 (in place of EGTA),NaCl 57, and 0 or 500 μM oxotremorine, and the enhancement of K^+-ERDA was assessed. DA release was then quantitated by HPLC coupled to electrochemical detection. Data were expressed as *p* mol/mg protein as determined by the Lowry procedure (Lowry et al., 1951). We have previously shown that there is a significant decrease in DA release 3–180 days following exposure to as little as 0.10–0.50 Gy of 600 MeV ^{56}Fe particles (Joseph et al., 1992).

3. Results

For each behavioral measure, between-subjects analysis of variance (ANOVA) models comparing the four radiation groups were performed using Systat (SPSS, Inc., Chicago, IL) to test for statistical significance at the $p < 0.05$ level. Days or trials, when appropriate, were included in the model as a within-subjects variable.

3.1. Amphetamine-induced conditioned taste aversion learning

As shown in Fig. 1, there were no significant effects of proton radiation on CTA. All groups of rats showed equivalent percent sucrose intakes from the conditioning day to the test day following injection of amphetamine. In contrast to the results obtained with rats exposed to ^{56}Fe particles, exposing rats to up to 4.0 Gy of 250 MeV protons did not disrupt the acquisition of the dopamine-mediated CTA produced by injection of amphetamine. Previously, we have shown that exposing rats to 1 Gy of ^{56}Fe particles blocks the acquisition of amphetamine-induced CTA (i.e., greater sucrose intake than non-irradiated rats) 3 days following irradiation (Rabin et al., 1998). Amphetamine-induced CTA is dependent upon the integrity of the central dopaminergic system.

3.2. Morris water maze

Exposing rats to protons produced no consistent alteration in water maze performance (Fig. 2). Overall, there were no significant differences in latency or swim speed to find the platform when all groups were analyzed. Individual analyses revealed that rats irradiated with 4.0 Gy showed an increased latency to find the hidden platform on Day 1 ($p < 0.05$), but by Day 2 onward were identical to controls. In fact, the difference on Day 1 was due to an increased latency to find the platform on the initial trial only (Trial 1) in the 4.0 Gy group; there were no significant differences from controls in subsequent trials. Rats irradiated with 1.5 Gy

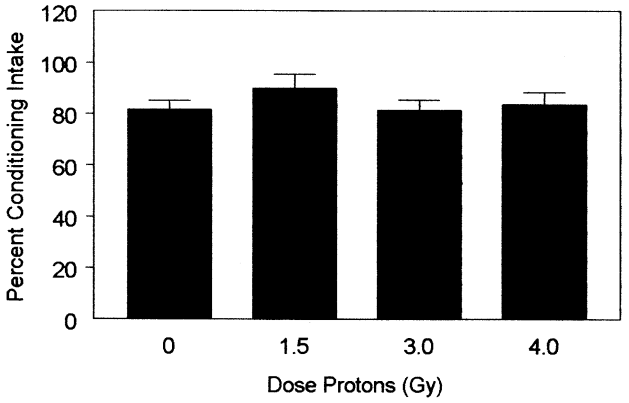

Fig. 1. Effects of exposure to 250 MeV protons (0, 1.5, 3.0, or 4.0 Gy) 3 days following radiation exposure on amphetamine-induced conditioned taste aversion in rats. Data is shown as percent conditioning intake, which is calculated as test day sucrose intake as a percent of conditioning day intake.

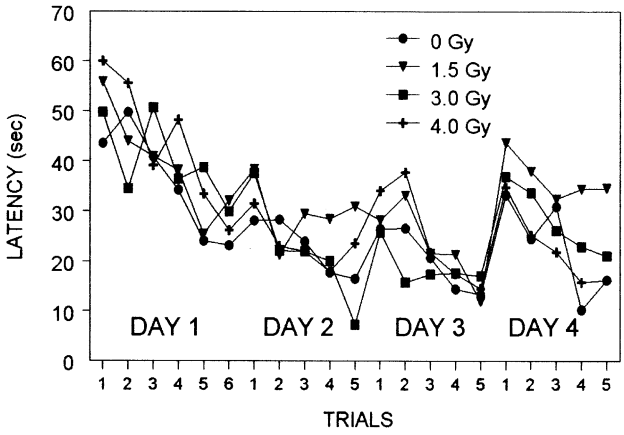

Fig. 2. Effects of exposure to 250 MeV protons (0, 1.5, 3.0, or 4.0 Gy) 6 weeks following radiation exposure on spatial learning and memory as assessed with the Morris water maze. Data shown is the latency (s) to find the hidden platform over the various days and trials of the experiment.

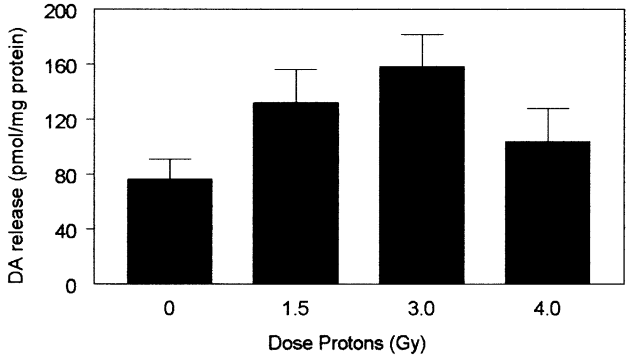

Fig. 3. Effects of exposure to 250 MeV protons (0, 1.5, 3.0, or 4.0 Gy) on dopamine release (p mol/mg protein) from the striatum of rats.

demonstrated impairments in re-learning compared to the control group as shown by increased latencies on the reversal day (Day 4), when the platform was moved to the opposite quadrant ($p < 0.05$). However, the difference between the groups was due to an increase on Trial 4 only. These results are in contrast to those obtained with rats following exposure to ^{56}Fe particles, in that ^{56}Fe-exposed rats show cognitive impairment compared to the control group as evidenced by increased latencies to find the hidden platform, particularly on the reversal day during re-learning (Trials 2 and 3).

Furthermore, spatial learning and memory were not disrupted as all groups performed equally well on the probe trials (swim with no platform). Dependent measures on the probe trials included percent time spent searching in each of the four quadrants of the pool; number of crossings of, latency to, and percent time in the region of the pool marking the exact position and surface area of the previous location of the hidden platform; and percent time spent in the various zones of the pool. The fact that there were no differences between the groups on these measures showed that all groups equally utilized spatial strategies to find the platform. This result is in contrast to that seen following ^{56}Fe particle radiation, since animals radiated with HZEs utilized non-spatial strategies during the probe trials as shown by less time spent in the platform quadrant; fewer crossings of and less time spent in the previous platform location; and longer latencies to the previous platform location.

3.3. Dopamine release

Exposing rats to 1.5, 3.0 or 4.0 Gy of 250 MeV protons produced no significant alterations in DA release (Fig. 3). In fact, compared to control animals, all groups of irradiated animals, particularly those exposed to 1.5 and 3.0 Gy, showed a slight increase in dopamine release, but these differences did not reach significance. This result is in contrast to that seen with ^{56}Fe particles, in which DA release is significantly decreased following radiation. Current results indicate that exposure to up to 4.0 Gy of high energy protons does not affect the functioning of the dopaminergic system.

4. Discussion

This study showed that irradiation with 1.5–4.0 Gy of 250 MeV protons did not alter neurochemical or behavioral endpoints in rats measured in this study. Neither dopaminergic functioning measured via oxotremorine-enhancement of K^+-evoked release of dopamine from striatal slices, amphetamine-induced CTA learning, nor spatial learning and memory as measured by the MWM was significantly disrupted following radiation exposure. These differences are in contrast to those seen following exposure to heavy particles, primarily in animals irradiated with ^{56}Fe radiation in which there are deficits in dopamine release (Joseph et al., 1992), amphetamine-induced conditioned taste aversion learning (Rabin et al., 1998, 2000), and spatial learning and memory (Shukitt-Hale et al., 2000, 2003).

It has been shown that for behavioral endpoints that are mediated by central systems (such as those seen in this study and our other studies), the effects of exposure to ^{56}Fe particles are not seen following exposure to lower linear energy transfer (LET) γ rays or fission spectrum neutrons (Rabin et al., 1998). The relative biological effectiveness (RBE) of high energy protons is not significantly greater than that of γ rays (Ando et al., 2001), so it is not surprising that exposure to protons does not affect the behavioral and neurochemical endpoints measured in this study since γ rays, even when delivered at a dose greater by a factor of 100, did not produce the same deleterious behavioral effects as ^{56}Fe particle irradiation (Rabin et al., 1998, 2000).

Therefore, there are significant differences both in the effectiveness and in the mechanisms by which exposure to heavy particles produces these behavioral effects compared to low LET types of radiation such as protons (Hodges et al., 1998; Lamproglou et al., 1995; Shukitt-Hale et al., 2000; Winsauer et al., 1995). Deficits in behavior and neurochemistry are seen with a much lower dose of heavy particles (e.g., 1.5 Gy of 1 GeV/n ^{56}Fe, Shukitt-Hale et al., 2000) compared to the higher doses (20–30 Gy) needed for low LET types of radiation (Hodges et al., 1998; Lamproglou et al., 1995). When examining the cognitive effects of exposure to ^{56}Fe particles, they are seen much earlier following irradiation (e.g., 30 days) (Shukitt-Hale et al., 2000) compared to deficits in water maze performance following other types of radiation, which are not observed until 200–280 days following exposure (Hodges et al., 1998; Lamproglou et al., 1995). The doses used in these latter experiments, and the interval between irradiation and behavioral testing, suggest that behavioral effects were secondary to the effects of the exposure on the vascular system and on the white matter (Prasad, 1995; Tiller-Borich et al., 1987). In contrast, work with heavy particles suggests that the deficits in behavioral performance result from the direct effects of the particles on neural function (Joseph et al., 1998; Rabin et al., 1998, 2000). We have shown (Rabin et al., 1998, 2000) that for behavioral endpoints that are mediated by peripheral systems, the RBE of different types of radiation form a continuum, i.e., as LET increases, so does RBE (quantitative differences). In contrast, for behaviors mediated by the central nervous system, the effects of ^{56}Fe particles are qualitatively different and more severe than those seen for other types of irradiation, and it is not possible to determine the RBE of ^{56}Fe for these specific endpoints (Rabin et al., 1998, 2000).

These results of this study with regard to protons also agree with those from another one of our studies (Rabin et al., 2002b) which showed that rats exposed to 4 Gy of protons or 1 Gy of ^{56}Fe particles responded similarly to controls in the ability to make an ascending fixed-ratio operant response. In contrast, rats exposed to 2 Gy of ^{56}Fe particles failed to increase their rate of responding at ratios greater than fixed ratio-20, indicating that they could not respond appropriately to increasing work requirements (Rabin et al., 2002b). Our results are therefore consistent with other experiments showing that the relative behavioral effectiveness of high energy protons is not significantly greater than that of γ rays (Ando et al., 2001; Rabin et al., 1998).

There have been some studies which have shown deleterious effects of proton irradiation. In one investigation, it was found that exposure to 155 MeV protons, 2–8 Gy at 1 Gy/min or 22–101 Gy at 20 Gy/min resulted in degeneration of astrocytes and other glial cells, but not neurons, in different areas of the brain (Switzer et al., 1994). Thus far, astrocytes per se have not been shown to be implicated in learning and memory, therefore, we would not expect to see changes in the behavior measured in this study at these proton doses. Another study using C57BL/6 mice indicated that exposure to 250 MeV (3 or 4 Gy) proton irradiation produced transient direct deficits in spontaneous open-field locomotor activity, acoustic startle habituation, and rotorod performance (Pecaut et al., 2002). However, if left to recover for 2 weeks following exposure, only rotorod performance at 26 rpm was impaired (Pecaut et al., 2002). In contrast, ^{56}Fe irradiation produces longer-lasting effects on the dopaminergic system, as many behaviors fail to show recovery of function following exposure (e.g., Joseph et al., 1992; Rabin et al., 2003). In our current study, amphetamine-induced CTA was tested 3 days following radiation, while cognitive performance and dopamine release were performed at 6 and 11 weeks, respectively. These testing times are consistent with our studies using ^{56}Fe irradiation, in which we see deficits. Again it appears as though proton irradiation does not produce the same deleterious behavioral and neurochemical effects as ^{56}Fe particle irradiation. Another possible explanation for the transient effects seen by Pecaut et al. (2002) following proton irradiation is that they used mice, while we used rats in the current study.

The significance of the studies on the neurochemical and behavioral effects of exposure to high energy protons lies in the fact that protons can make up a significant portion of the radiation spectrum. To date, our research has indicated that exposure to non-lethal levels of protons (up to 4.0 Gy) does not significantly affect either central nervous system dopaminergic function or behavior. While the interpretation of results which fail to obtain significant differences between the rats exposed to protons and the control rats is problematical, it may be that, despite their prevalence in space, exposure to protons may not represent a significant problem for astronauts in terms of their ability to perform required tasks and successfully complete mission requirements.

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